USPQ2d 1464 (Fed. Cir. 1999). Because the Examiner notes that "Applicant has not enabled the breadth of the claimed invention in view of the teachings of the specification because the claims encompass a method for human therapy" (p. 2, paragraph 5 of the January 26, 2001 Office Action), it is Applicants' interpretation that this is a rejection based on the scope of enablement and not a general enablement rejection.

As such, the issue is whether the specification enables the full scope of the claimed invention. "The scope of the claims must be less than or equal to the scope of enablement. The scope of enablement, in turn, is that which is disclosed in the specification plus the scope of what would be known to one of ordinary skill in the art without undue experimentation." *National Recovery Technologies Inc. v. Magnetic Separation Systems,* 49 USPQ2d 1671 (Fed. Cir. 1999) citing In re Goodman, 11 F.3d 1046, 1049-1050, 29 USPQ2d 2010, 2013 (Fed. Cir. 1993). That is, "[t]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. *National Recovery Technologies Inc. v. Magnetic Separation Systems,* 49 USPQ2d 1671 (Fed. Cir. 1999) citing *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

To this end, Applicants respectfully remind the Examiner that the claims should be considered as a whole when determining exactly what subject matter is encompassed by the claims. MPEP 2164.08. Moreover, Applicants note that while the PTO must give claims their broadest reasonable interpretation, this interpretation must be consistent with the one that those skilled in the art would reach. *In re Cortright*, 49 USPQ2d 1464 at 1467 citing *In re Morris*, 127 F.3d 1048, 1054, 44 USPQ2d 1023, 1027 (Fed. Cir. 1997). Claim 1 is drawn to a method for killing a target cell in a mammalian host wherein the method comprises introducing a conjugate into said host in sufficient amount to kill the target cells, wherein said conjugate comprises a moiety other than an antibody or fragment thereof specific for a surface protein joined to a selective moiety capable of binding to said effector system to form a cell killing complex, with the proviso that when said selective moiety binds to a T-cell, (a) it binds to the T-cell receptor and (b) said moiety specific for a surface protein is a ligand for a receptor; wherein said effector system comprises (1) antibodies specific for said selective moiety and an antibody dependent

cytotoxic system comprising at least one effector agent or (2) a T-cell, whereby when said conjugate is bound to both of said target cell and said effector agent, said cell is killed.

The specification fully enables the skilled artisan to practice the invention.

The Examiner asserts that undue experimentation would be required of one skilled in the art to practice the instant invention using the teaching of the specification. Applicants respectfully disagree with this characterization. The Examiner notes that the claimed invention encompasses a method for treatment of human disease *in vivo* and that this is not enabled by the specification. Applicants respectfully submit that the instant specification combined with the knowledge of one of ordinary skill in the art at the priority date provides a disclosure that fully enables the scope of the pending claims. That is, the skilled artisan upon reading the present specification would be able to practice the claimed invention, *i.e.* a method of killing a target cell in a mammalian host, without undue experimentation.

The specification provides several examples of various conjugates that could be made, as well as detailed methods for preparing and assaying such conjugates both *in vitro* and *in vivo*. For example, in Example 3 on pages 17-18 of the specification, Applicants describe a conjugate comprising an α-Gal antigen linked to folate that is capable of binding *in vitro* to tumor cells expressing a high affinity folate receptor and killing those cells through anti-α-Gal antibody-dependent cell lysis. To demonstrate the feasibility of this hapten approach in a rodent model, where the animal naturally expresses α1,3-galactosyl transferase and thus would not have the requisite antibodies, an alternative conjugate was synthesized. Specifically, Example 4 on pages 18-25 of the specification describes the preparation and testing of a conjugate comprising an $F(ab')_2$ fragment of polyclonal anti-thymocyte globulin (ATG) bound to fluorescein isothiocyanate (FITC), where the FITC serves as a model hapten. Applicants have successfully employed similar FITC conjugates in a mouse allotransplantation model and in a syngeneic murine tumor model. *See*, Lussow *et al.*, *Transplantation 62*:1703-1708 (1996), Lussow *et al.*, *Transplant. Proc. 28*:576-77 (1995), Lussow *et al.*, *J. Immunotherapy 19*:257-265 (1996) (Applicants are submitting a copy of the foregoing publications in a supplemental Information

Disclosure Statement). These results provide clear and unambiguous *in vivo* support for the presently-claimed invention.

Moreover, the specification is not to be viewed in a vacuum. Rather, the specification is to be viewed through the eyes of one of ordinary skill in the art. The Examiner notes that the technological area is unpredictable and as such the specification is not enabling. However, Applicants submit that this in but one factor to consider in making a determination regarding enablement. Additional factors include the level of skill in the art, the guidance of the disclosure, the quantity of experimentation necessary, the presence or absence of working examples, the state of the prior art, the nature of the invention and the breadth of the claims. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1989).

To this end Applicants note that the level of skill in the art is high. That is, the skilled artisan in the field of immunology and in particular the field of therapeutics will likely have a Ph.D or M.D. Degree and experience in the field. Further, the state of the prior art at the time of filing the application was advanced. That is, there was a significant body of literature regarding therapeutic conjugates, as evidenced by the Information Disclosure Statements and 892's of record in the present application. Moreover, the specification provides significant disclosure as to how to make the conjugates of the invention and how to practice the invention. In this regard, Applicants note that "a considerable amount of experimentation is permissible, if it is merely routine or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed." *PPG Industries Inc. v. Guardian Industries Corp.*, 75 F.3d 1558, 1564, 37 USPQ2d 1618, 1623 (Fed. Cir. 1996) citing *Ex parte Jackson* 217 USPQ 804, 807 (1982). There are extensive teachings in the specification to enable one of skill in the art to practice the claimed method of killing a target cell in a mammalian host.

The Examiner appears to be suggesting that Applicants must provide *in vivo* data from clinical trials in humans before a patent can be issued on the claimed invention. Applicants submit, however, that this requirement is quite unreasonable, especially given the Patent Office examination guidelines (and the legal analysis supporting those guidelines) with regard to

enablement, that is, whether the specification and knowledge of the skilled artisan combine to enable the skilled artisan to practice the claimed invention without undue experimentation. Applicants point out that the standard for enablement is a "reasonable correlation" between the data and the assertions such that one skilled in the art would have a "reasonable" degree of confidence of success in practicing the claimed invention. MPEP 2164.04 and 2164.05. As noted above, in light of the skill in the art and the extensive teachings in the specification, Applicants submit that it would not require undue experimentation for the skilled artisan to practice the invention as claimed.

The references cited by the Examiner in support of the enablement rejection do not mandate a different result. Basically, the Examiner notes that Tueveson *et al* and Osband *et al* teach that rodent models of transplantation are not predictive of results in humans. Borrebaeck *et al* is cited as support for the Examiner's opinion that anti-α-gal antibodies would clear a targeting conjugate containing the α-gal antigen, as opposed to killing the cell to which the conjugate is targeted. Waldmann is cited in support of the position that the "magic bullet" of antibody therapy has proved elusive. Harris *et al* is cited for the proposition that there is little use for rodent antibodies for in vivo human therapy.

Initially, Applicants question the relevance of these references as applied to the presently pending claims. With respect to Harris, Applicants note that the presently pending claims do not use antibodies to bind to a target cell. Accordingly, this reference is inapplicable to the present claims. As to Waldmann, Applicants note that the claims are not limited to a "magic bullet". That is, the claims do not require that the target cell is killed while absolutely no other cells are killed. The specification explicitly addresses this issue at p.11, line 16 wherein it is noted that "[u]nique specificity is not required as long as there is a substantial preference for binding to the target cells." Thus, the Waldmann reference is not applicable to the issue of enablement of the presently claimed invention. With respect to Tueveson *et al.* and Osband *et al.*, Applicants submit that the fact that rodent models of transplantation are not always predictive of results in humans does not preclude or weigh against a finding of enablement of a method of killing a target cell in a mammalian host. As noted above, it is the job of the FDA to govern safety and

efficacy of human treatment, not the Patent Office. The test for the patent office is whether the specification provides the skilled artisan with a reasonable degree of confidence of success in practicing the claimed invention. As to Borrebaeck, again Applicants submit that Borraebaeck describes treatment of humans with mouse antibodies that contain α-gal antigen. Borraebaeck notes a correlation between the presence of α-gal antigen and half-life of mouse antibody. While Borrabaeck proposes that the presence of the α-gal antigen increases antibody clearance, there is no teaching in Borrabaeck to suggest that cells were not also killed. There is no reason that increased clearance and cell killing must be mutually exclusive. As such, Applicants submit that Borrabaeck is not relevant to the claimed method.

The Examiner also raises issues concerning the specificity of target cell killing. Namely the Examiner questions "how the method of the instant invention can inactivate target cells without also inactivating normal cells that express receptors" for the moiety specific for the target cell. In response Applicants note that no such specificity is required by the claims. In fact, countless treatments for human disease result in killing of target cells as well as "normal cells", *i.e.* cells that are not targeted for killing, such as the rigorous chemotherapy protocols routinely used in the treatment of cancer, the toxicities of which are well-known.

The Examiner also notes that Borrebaeck indicates that α-gal "antibodies are not found in mammals per se, but only in humans and old world monkeys. As such the Examiner notes that the conjugates could not be used in mammals per se. Applicants respectfully disagree.

Applicants draw the Examiner's attention to the language of the claim 1 which requires that the mammalian host have an effector system capable of binding the selective moiety. Applicants respectfully remind the Examiner that the claims should be considered as a whole when determining exactly what subject matter is encompassed by the claims. MPEP 2164.08. When the selective moiety is α-gal, therefore, the effector agent must be able to bind this moiety. However, as the Examiner notes, not all mammals have antibodies that can bind α-gal, i.e. the effector system of these animals is not capable of binding the α-gal selective moiety. As such, treatment of those mammals with a conjugate that contains α-gal as the selective moiety is

outside of the scope of the claimed method.

In sum, Applicants submit that the claims are fully enabled by the specification. That is, one of ordinary skill in the art upon reading the specification would be able to practice the invention as claimed without undue experimentation. The specification provides notable direction and guidance for preparing conjugates and assaying their activity in a method of killing a target cell in a mammalian host. Moreover, the level of skill in the art is high. Because the specification enables the full scope of the claims, Applicants respectfully request the Examiner to withdraw this rejection.

Response to Rejection Under 35 USC 102

Claims 1, 2 and 6 stand rejected under 35 U.S.C. § 102(b) as anticipated by EP 0510949 (Pouletty). The Examiner notes that as a result of the decision of the decision of the Board of Appeals in serial number 07/690, 530 ('530 application), the present application is not entitled to the filing date of the '530 application. As such, Pouletty anticipates claims 1, 2 and 6. Applicants respectfully traverse the rejection.

As to the Examiner's position that the presently claimed invention is not entitled to the filing date of the '530 application, Applicants respectfully disagree. Notwithstanding the decision of the Board, Applicants maintain the enablement of the claimed method. As such, Applicants submit that Pouletty is not prior art against the present application.

Moreover, Applicants note that to anticipate a claim in a patent application, a prior art reference must teach every element of the claim (MPEP 2131). In addition, the prior art reference must place the public in possession of the invention. That is, the prior art reference must contain an enabling disclosure (MPEP 2131). As such, Applicants submit that even if the Examiner is correct and the present claims are not entitled to the '530 filing date, the Examiner's position must be that '530 is not enabling. Accordingly, Pouletty (which is the European publication of the '530 application) cannot anticipate the present claims because it is not an enabling reference.

Accordingly, Applicants submit that the present claims are entitled to the filing date of

the '530 application and respectfully request the Examiner to withdraw the rejection over Pouletty. In the alternative Applicants respectfully request the Examiner to withdraw the rejection over Pouletty because it is not an anticipatory reference.

Claim 1 is rejected under 35 U.S.C. § 102(b) as being anticipated by EP 0180171 (Kranz et al.). The Examiner indicates that Kranz et al. teach a method for lysing target cells by administering a conjugate that includes a moiety specific for a target cell and a selective moiety that binds the T-cell receptor. Applicants respectfully traverse the rejection.

Kranz *et al.* is about making target cells susceptible to lysis by cytotoxic T-lymphocytes (CTL). The document teaches that one can do this by use of an antibody for the T-cell receptor (TcR) which antibody is **bound** to the target cell. Thus, the document teaches the covalent attachment (by use of 0.1% glutaraldehyde) of a monoclonal antibody called IB2 that recognizes the TcR of a CTL clone, clone 2C. Cells (R1.1 and R1.E cells) not normally lysed by CTL clone 2C were stated to be convertible into target cells by use of the mAb to the CTL clone receptor. Although this statement of effect was made, it is to be noted that no results are provided in the document.

Kranz *et al.* only provides a technical teaching in relation to the covalent attachment of mAb IB2 to target cell. Kranz *et al.* at page 3 state that anti-TcR antibody may be bound to target cell either directly or indirectly by means of a linker molecule. They go on to state that the linker could be another antibody against an antigen on the targeted cell surface, a hormone that binds to a receptor on the targeted cell surface, or a carbohydrate such as galactose which binds to receptors on liver cells. Importantly, however, except for this vague and unsupported generalization of the idea of attaching antibodies for the TcR to a target cell, no actual disclosure is made of conjugates. In Kranz *et al.* the effective reagent is disclosed as being an antibody and the only supported teaching is of direct coupling to target cells.

Accordingly, Kranz *et al.* can at best be construed as providing a teaching that one can inactivate target cells *in vitro* by **coupling an anti-TcR antibody to them** to make them susceptible to lysis by cytotoxic T lymphocytes. Kranz *et al.* has no disclosure of achieving

target cell inactivation by use of an antibody effector system. The disclosure in Kranz *et al.* is only relevant to the situation where the "selective moiety" binds to a T cell. There is clearly no proper disclosure of employment of conjugates to cross link *in vitro* an effector system to a target cell. As noted above, for a reference to be anticipatory, it must not only contain each and every element of the claims, but it also must be an enabling reference. Applicants submit that Kranz fails to provide an enabling disclosure.

Applicants also respectfully draw the Examiner's attention to *Ex parte Kranz*, 19 USPQ2d 1216 (BdPatApp&Int, 1990). The patent application in question in *Ex parte Kranz* was U.S. Serial No. 666,880 and contained claims drawn to a method of making a targeted cell susceptible to lysis by a cytotoxic T lymphocyte comprising attaching an antibody specific for determinants of an antigen specific cytotoxic T lymphocyte receptor to a targeted cell not having major histo-compatibility complex proteins recognized by the cytotoxic T lymphocyte receptor. This is the application on which Kranz *et al.* is based and to which it claims priority.

On appeal of the examiner's final rejection of the claims, the Board reversed the obviousness rejection over prior art, but levied a new rejection of the claims under 35 U.S.C. 112, first paragraph noting that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. Noting that none of the work depicted in the specification is directed to in vivo experimentation and that the methods disclosed were clearly unavailable for use in vivo, the Board held that the specification did not enable the claims.

In view of the foregoing, Applicants respectfully submit that Kranz *et al.* is also not an anticipatory reference because it fails to contain an enabling disclosure, and therefore Applicants request that the anticipation rejection based on this reference be withdrawn as well.

Claims 1, 2 and 6-8 are rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 5,334,379 to Pillai *et al.* The Examiner argues that while Pillai *et al.* is silent with respect to lysing target cells, the lysis will inherently occur because the claimed method recites

the same steps disclosed by Pillai *et al.* Applicants respectfully traverse the rejection, since Pillai fails to teach each and every element of the claimed invention.

Specifically, Applicant's conjugate as recited in Claim 1 requires 1) a "targeting" moiety specific for a surface protein on the target cell, joined to 2) a selective moiety which must be capable of binding to the host's endogenous effector system to form a cell killing complex. Pillai *et al.* fail to teach or suggest such a conjugate. The conjugates described by Pillai *et al.* are designed and intended to increase the immunogenicity of non- or weakly immunogenic antigens such as polysaccharides. *See. e.g.*, col. 3, lines 49-64. Thus, Pillai *et al.* teach that the carbohydrate-containing antigen can become immunogenic or more so by virtue of conjugation to a cytokine, lymphokine, hormone or growth factor. *Id.* By itself, however, the carbohydrate-containing antigen is incapable of being either the targeting moiety or the selective moiety required by the present claims.

Applicants further dispute the Examiner's contention that practicing the method disclosed in Pillai *et al.* will inherently result in the lysing of target cells as presently claimed. Administering the conjugates described by Pillai *et al.* will not result in the conjugate binding to both the target cell and the effector agent, thereby directly inactivating the target cell, since the carbohydrate-containing antigen does not bind to either a specific target cell or to an effector agent as required of the moieties in the presently-claimed conjugate. In Pillai *et al.* the antigen is simply carried along with the more immunogenic component of the conjugate, *e.g.* the cytokine, and allegedly serves to stabilize this component. The Pillai *et al.* conjugates do not directly lyse target cells by forming a cell-killing complex. In view of the foregoing significant differences between the components of the conjugates and their intended use, Applicants respectfully submit that the disclosure in Pillai *et al.* is largely inapposite. Accordingly, Applicants respectfully request the Examiner to withdraw the rejection.

Response to Rejection Under 35 U.S.C. § 103

Claim 4 stands rejected as being unpatentable over EP 0510949 (Pouletty) in view of the prior art disclosed in the specification (p. 9, first complete paragraph). The Examiner suggests

that one of ordinary skill in the art would have a reasonable expectation of success in practicing the invention because α-gal antibodies were known in the art and "would have been strong mediators of antibody mediated lysis of target cells" (see paragraph 37 of November 27, 1996 Office Action). As such, the Examiner concludes that it would have been prima facie obvious to one of ordinary skill in the art to use the α-gal antigen in the method taught by Pouletty. Applicants respectfully traverse the rejection.

As the Examiner is aware to establish a *prima facie* case of obviousness under 35 U.S.C. § 103, the Examiner must demonstrate that the prior art provides one of ordinary skill with a suggestion or motivation to modify or combine the teachings of the references relied upon by the Examiner to arrive at the claimed invention. M.P.E.P. § 2143.

Applicants submit that the Examiner has failed to provide any motivation or suggestion from the cited references demonstrating the desirability of combining their teachings. To this end, Applicants remind the Examiner that "[a]lthough a prior art device 'may be capable of being modified to run the way the apparatus is claimed, there must be a suggestion or motivation in the reference to do so'" (M.P.E.P. § 2143.01, *citing In re Mills*, 16 USPQ2d 1430,1432 (Fed. Cir. 1990)). Thus, while the Examiner suggests that it would have been obvious to consider the references, there is no indication of any teaching in the references that would have motivated one of ordinary skill in the art to combine the references to arrive at the claimed invention. Applicants respectfully remind the Examiner that evidence of a motivation to combine references requires "actual evidence: That is, the showing must be clear and particular .... Broad conclusory statements regarding the teaching of multiple references, standing alone, are not 'evidence.'" *In re Dembiczak*, 50, USPQ2d 1614, 1617 (CAFC, 1999). As such, Applicants submit that claim 4 is both novel and nonobvious in light of the cited art. Applicants therefore respectfully request the Examiner to withdraw the rejection.

Claims 1, 7 and 8 are rejected under 35 U.S.C. § 103 as being unpatentable over Kranz *et al.* in view of U.S. Patent No. 5,298,395 to Park *et al.* Kranz describes a method for making a target cell susceptible to lysis by contacting the cell with a conjugate that bridges a T-cell to the

target cell. Park teaches purified ligands including cytokines such as Il-2 that can be conjugated to functional moieties. The Examiner suggests that one of ordinary skill in the art would have been motivated to combine the references because Kranz teaches that growth factors can be the moiety specific for a surface protein and that Park teaches conjugates that include growth factors including Il-2. Applicants respectfully traverse the rejection.

There are three requirements to establish a *prima facie* case of obviousness. The Examiner must demonstrate that the prior art provides one of ordinary skill with a suggestion or motivation to modify or combine the teachings of the references relied upon by the Examiner to arrive at the claimed invention. The combination must provide the skilled artisan with a reasonable expectation of practicing the invention as claimed and the combination must set forth all elements of the claims. M.P.E.P. § 2143.

Applicants submit that neither reference provides the requisite motivation for the Examiner's proposed combination, particularly since the two disclosures are directed to entirely different goals. As discussed above, Kranz *et al.* is directed primarily to the covalent attachment of anti-TcR antibodies directly to a target cell to achieve lysis, while Park discusses recombinant ligand reagents such as cytokines for use in detecting, separating and purifying cells having receptors for such ligands. Given their disparate goals and procedures one of skill in the art would not be motivated to combine the two disclosures in an attempt to obtain the presently claimed invention. Applicants therefore submit that a prima facie case of obviousness has not been met. Moreover, even if the two disclosures are combined, albeit improperly, one does not arrive at the presently-claimed method, wherein a cell-killing complex is formed by a conjugate having a targeting moiety and a selective moiety, when the conjugate binds to both the target cell and an effector agent. Applicants respectfully request the Examiner to withdraw the rejection.

CONCLUSION

For the foregoing reasons, Applicants submit that the claims are now in condition for allowance. A notice to that effect is respectfully requested. Should the Examiner be of the opinion that any outstanding matters exist which may be addressed by way of a telephone

conference call, he is invited to contact the undersigned to discuss such matters.

Respectfully submitted,

FLEHR HOHBACH TEST
ALBRITTON & HERBERT LLP

By _____
Todd A. Lorenz
Reg. No. 39,754

Four Embarcadero Center
Suite 3400
San Francisco, CA 94111-4187
Telephone: (415) 781-1989

Appendix A

Pending claims

1. A method for killing a target cell in a mammalian host comprising said target cell and an endogenous cytotoxic effector system comprising a least one effector agent, said method comprising:

introducing a conjugate into said host in sufficient amount to kill the target cells, wherein said conjugate is characterized by comprising a moiety other than an antibody or fragment thereof specific for a surface protein joined to a selective moiety capable of binding to said effector system to form a cell killing complex, with the proviso that when said selective moiety binds to a T-cell, (a) it binds to the T-cell receptor and (b) said moiety specific for a surface protein is a ligand for a receptor; wherein said effector system comprises (1) antibodies specific for said selective moiety and an antibody dependent cytotoxic system comprising at least one effector agent or (2) a T-cell, whereby when said conjugate is bound to both of said target cell and said effector agent, said cell is killed.

2. A method according to Claim 1, wherein said selective moiety is a blood group antigen, an antigen to which the host has been previously sensitized or a superantigen.

4. A method according to Claim 2, wherein said selective moiety binds to anti-α-gal antibodies.

6. A method according to Claim 1, wherein said moiety specific for a surface protein is a small organic molecule having a molecular weight of more than 100 and less than about 5000 daltons.

7. A method according to Claim 1, wherein said moiety for said surface protein is a ligand for a cytokine surface membrane protein receptor of said target cell.

8. A method according to Claim 7, wherein said ligand is IL-2.